

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: DeStefano, G. et al.) Confirm. No.: 7531
Serial No.: 10/804,710) Art Unit: 1616
Filed: March 19, 2004) Examiner: Haghghatian, Mina
For: Formulation for a metered dose inhaler using hydro-fluoro-alkanes
as propellants
Docket No.: 9/277 (539/168)

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF GEORGE DESTEFANO UNDER 37 C.F.R. § 1.132

I, George DeStefano, declare:

1. This declaration is submitted to present evidence in response to the Office Action dated October 4, 2007 in the above-referenced patent application.

2. I am employed at Boehringer Ingelheim Pharmaceuticals, Inc. I am an inventor in the above-referenced patent application.


3. It is noted that the Office Action contains a rejection of claims 5 and 7 under 35 U.S.C. § 103(a) as being unpatentable over Lewis et al. (EP 1219293) in view of Jager et al. (WO 9413262), and of claims 1-7 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Pat. No. 6,423,298 in view of Lewis et al. The documents submitted herein in the attached pages provide additional experimental data showing the criticality of the claimed water content in the claimed formulations.

4. The following Analytical Reports provide support for the criticality of the water content in suspension formulations (Analytical Report, *Results for In Use 6 Hour Delay Single Actuation Reproducibility Study for Ipratropium Bromide/Albuterol Sulfate (HFA-134a) Inhalation Aerosol, with Water Contents Ranging from Inherent Water to 2500ppm*,

File No. AR-030012, February 5, 2003, Boehringer Ingelheim Pharmaceuticals Inc.; Analytical Report, *Evaluation of the Effect of Water on Single Actuation Reproducibility for Ipratropium Bromide/Albuterol Sulfate (HFA-134a) Inhalation Aerosol 0.021/0.120 mg TTV, 10 mL Equipped with the Bepak Valve Actuated using at Patient In-Use Testing Scheme*, Report No. AS/C-03004, January 28, 2003, Boehringer Ingelheim Pharmaceuticals Inc.). The data presented in Report No. AS/C-03004 show that a water concentration of 1500 ppm and greater (equivalent to 0.15% water content) in a suspension formulation containing albuterol sulphate and ipratropium bromide is needed to ensure that the single actuation reproducibility difference does not impact the product (see Abstract, Report No. AS/C-03004). File No. AR-030012 shows that water content of 300 to 1200 ppm (equivalent to 0.03 to 0.12% water content) in a suspension formulation containing albuterol sulphate and ipratropium bromide results in poor reproducibility, while a water content of 1500 to 2500 ppm (equivalent to 0.15 to 0.25% water content) exhibited good reproducibility (page 29, File No. AR-030012). This shows that the water content of the suspension formulation is a critical parameter in the single actuation reproducibility over time.

5. The Analytical Reports demonstrate the criticality of the water content in suspension formulations to achieve single actuation reproducibility of inhalants. The critical range of water content in a suspension formulation containing albuterol sulphate and ipratropium bromide to achieve reproducibility is from 0.13% and 0.25%.

6. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the likes so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patents issuing thereon.


George DeStefano
Date: March 10, 2008



**Boehringer
Ingelheim**

Report Number:

AS/C-03004

**ANALYTICAL SCIENCES DEPARTMENT
CONTRACT LABORATORY REPORT**

Title: Evaluation of the Effect of Water on Single Actuation Reproducibility for Ipratropium Bromide/Albuterol Sulfate (Inhalation Aerosol 0.021/0.120 mg TTV, 10 mL Equipped with the Bepak Valve Actuated using at Patient In-Use Testing Scheme)

Laboratory: Cardinal Health RTP

Report Date: Jan. 28, 2003

**Product/
Project:** Ipratropium Bromide/Albuterol Sulfate
Inhalation Aerosol 0.021/0.120 mg TTV, 10 mL

BI Project Code:

**Person Submitting
Report for Archival:** Paul D. Curry, Jr., Ph.D.

**Contract Lab
Protocol #:**

**Date Report
Archived:** 1/29/03

Key Words: Ipratropium Bromide/Albuterol Sulfate (Inhalation Aerosol 0.021/0.120 mg TTV, 10 mL, Effect of Water, Single Actuation Reproducibility, Bepak Valve, Patient In-Use)

Abstract: It is well known that additional water can have a detrimental effect on the performance of non-aqueous suspensions. This study was designed to study the impact of water on single actuation reproducibility (SAR) and to initially identify a minimum water concentration where the reproducibility is suitable. Other studies have shown low dose delivery for the first shot followed by a higher dose for the second for albuterol sulfate at low water concentrations. The addition of water to the formulation brings the dose for the individual actuation back to the target delivery. Ipratropium bromide does not show this behavior because it is in solution in this formulation unlike albuterol sulfate which is suspended.

This study demonstrates the same behavior. The data would indicate that water concentration of 1500 ppm and greater are needed to ensure that the single actuation reproducibility difference does not impact the product.

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7501

Theoretical Water Content: Inherent

Analysed: Brook White

Activation Number	Test	Inverted									
		Can 1		Can 2		Can 3		Can 4		Can 5	
		Alb SQ4	IPB	Alb SQ4	IPB	Alb SQ4	IPB	Alb SQ4	IPB	Alb SQ4	IPB
25	SAR	113.13	20.56	118.21	20.85	115.17	20.64	117.57	20.63	122.36	21.72
26	SAR	113.42	19.74	112.10	19.45	117.79	20.54	117.26	20.34	119.82	21.42
33	SAR	71.03	19.66	66.59	19.61	90.17	19.95	62.84	19.43	82.38	19.42
34	SAR	245.57	20.14	202.70	19.47	216.22	19.59	238.14	21.24	214.94	20.25
45-46	Dose	159.74	19.46	139.27	18.83	144.63	19.52	169.23	19.22	149.47	19.76
69	SAR	60.95	19.29	78.53	19.87	76.67	19.34	70.93	18.94	128.19	18.60
70	SAR	240.53	20.28	237.87	19.34	256.88	20.88	232.40	20.84	222.82	21.00
105-106	Dose	133.76	19.27	95.46	19.54	95.94	20.03	92.92	19.78	95.99	19.87
129	SAR	169.42 ¹	19.62 ¹	57.22	19.31	79.18	19.95	69.29	18.84	56.62	18.79
130	SAR	161.63 ¹	19.62 ¹	181.90	19.69	156.13	20.43	177.50	20.78	161.25	19.90
165-166	Dose	103.76	19.55	101.53	19.61	104.51	20.45	100.96	19.96	92.65	19.65
187	SAR	87.48	19.52	58.20	25.05	47.18	19.52	57.62	19.52	92.57	19.22
188	SAR	146.99	20.16	168.57	20.82	142.08	21.13	153.97	20.93	136.70	20.66

Alb SQ4 = Albuteol Sulfate

IPB = Ipratropium Bromide

SAR = Single Activation Reproducibility

Water Content (ppm)

Activation	Can 1	Can 2	Can 3	Can 4	Can 5
16-20	263	257	260	262	265
199-203	364	343	343	331	325

¹These values were confirmed by re-injection since they were not in trend with the data set. The re-injected samples yielded results of 167.16 and 18.81 µg for Albuteol Sulfate and Ipratropium Bromide respectively.

²These values were confirmed by re-injection since they were not in trend with the data set. The re-injected samples yielded results of 160.32 and 19.42 µg for Albuteol Sulfate and Ipratropium Bromide respectively.

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7501

Theoretical Water Content: Inherent

Analyst: Nichole Blynn

Activation Number	Test	Upright									
		Can 6	Can 7	Can 8	Can 9	Can 10	Can 11	Can 12	Can 13	Can 14	Can 15
25	SAR	114.77	20.53	121.29	21.97	121.83	21.73	115.84	20.69	121.53	21.52
26	SAR	119.57	20.87	118.26	20.88	117.92	22.26	121.20	21.46	119.29	21.36
33	SAR	39.60	19.58	47.68	20.48	42.23	20.70	40.38	20.39	47.37	20.29
34	SAR	164.26	19.83	155.10	19.75	156.82	19.18	169.58	19.66	156.61	19.84
45-46	Dose	98.77	19.56	99.56	19.85	99.69	20.45	104.71	20.18	98.57	20.05
69	SAR	46.50	19.64	50.59	19.16	41.45	19.82	50.31	20.04	52.55	20.33
70	SAR	153.93	19.89	157.65	20.68	159.42	19.32	150.98	18.73	158.94	20.84
105-106	Dose	88.03	18.82	96.15	20.00	94.30	19.59	92.94	19.42	106.61	20.44
129	SAR	51.96	20.29	55.25	20.24	50.28	12.78	89.13	61.90	78.36	17.70
130	SAR	150.76	20.17	141.95	19.57	142.01	19.74	130.40	18.61	136.65	20.80
165-166	Dose	94.23	19.57	102.94 ²	17.66 ²	101.73	18.17	99.60 ²	16.83 ²	98.36 ²	16.97 ²
187	SAR	48.15	20.44	60.41	20.65	42.98	20.22	46.04	20.68	60.89	22.05
188	SAR	149.23	20.66	140.19	20.92	150.85	21.02	152.92	20.66	138.40	21.78

Alt SO₄ = Alburel Sulfate

IPB = Ipratropium Bromide

SAR = Single Activation Reproducibility

Water Content (ppm)

Activation	Can 6	Can 7	Can 8	Can 9	Can 10
16-20	275	270	260	268	279
199-203	341	337	327	330	402 ¹

¹The analyst observed an unusually weak plume for all 5 activations.

²The analyst observed that the first activation sounded weaker than normal.

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7502

Theoretical Water Content: 800ppm

Analyst: Dan Mikla

Activation Number	Test	Inverted									
		Can 1		Can 2		Can 3		Can 4		Can 5	
25	SAR	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
26	SAR	116.85	20.57	118.69	20.61	116.57	20.81	117.72	20.74	112.33	19.75
33	SAR	116.44	19.92	118.78	20.30	113.46	19.87	118.76	20.62	110.60	19.21
34	SAR	79.59	20.67	92.27	20.84	66.80	20.18	80.28	20.41	69.10	20.04
45-46	Dose	145.92	19.89	140.63	19.98	151.68	20.06	143.55	20.54	145.53	19.59
69	SAR	110.49	19.82	108.81	20.23	111.42	20.15	108.24	20.16	106.46	19.49
70	SAR	78.14	20.17	70.83	20.56	108.78	18.75	96.90	19.75	64.81	19.97
105-106	Dose	160.24	20.01	152.88	20.09	140.17	19.57	151.44	19.79	147.23	18.80
129	SAR	108.82	19.64	112.10	19.69	109.69	19.58	108.86	19.80	106.69	19.31
130	SAR	68.67	20.47	73.18	20.45	77.48	20.10	72.12	20.29	99.65	18.57
139	SAR	156.79	19.58	167.49	20.08	148.12	19.88	154.79	19.99	134.07	18.99
165-166	Dose	112.93	19.43	111.55	18.86	100.26	19.74	104.20	20.03	100.62	19.23
187	SAR	67.20	21.10	103.12	19.25	95.01	20.05	95.15	19.83	92.73	19.36
188	SAR	147.90	20.39	124.55	20.32	123.27	19.63	131.34	20.49	116.31	19.92

Alb SO4 = Albiterol Sulfate

IPB = Ipratropium Bromide

SAR = Single Activation Reproducibility

Water Content (ppm)

Activation	Can 1	Can 2	Can 3	Can 4	Can 5
16-20	688	722	714	735	686
199-203	762	811	802	821	819

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7502

Theoretical Water Content: 800ppm

Analyst: Kathryn Johnson

Activation Number	Test	Upright									
		Can 6	Can 7	Can 8	Can 9	Can 10	Can 6	Can 7	Can 8	Can 9	Can 10
25	AB SO4	115.28	20.70	119.93	21.20	115.46	20.36	113.94	20.15	119.07	21.20
26	SAR	114.34	20.09	124.94	20.97	117.20	20.01	118.16	20.34	118.37	20.66
33	SAR	39.99	19.47	41.84	20.47	46.49	19.44	38.20	21.41	43.36	20.82
34	SAR	157.71	18.38	164.30	19.43	157.55	19.46	168.46	20.03	166.32	19.99
45-46	Dose	96.73	19.35	92.46	18.69	93.65	19.13	94.80	18.68	100.53	19.88
69	SAR	38.59	19.78	35.71	19.36	49.57	19.41	38.83	19.89	42.23	20.46
70	SAR	143.60	18.58	166.93	19.27	150.52	18.93	159.28	19.25	154.28	19.17
105-106	Dose	87.15	17.99	97.51	18.47	91.32	18.18	99.86	18.55	101.10	19.12
129	SAR	42.03	19.87	39.31	20.28	42.43	18.17	34.56	20.05	40.71	20.43
130	SAR	138.57	17.76	147.59	18.68	142.98	19.29	150.27	18.49	148.09	20.41
165-166	Dose	89.15	18.04	86.24	18.93	92.27	19.31	88.26	18.65	96.64	18.59
187	SAR	36.33	20.01	37.75	20.06	51.64	20.84	33.77	19.84	44.69	21.23
188	SAR	138.95	18.61	148.22	19.36	130.27	19.40	144.81	20.04	142.98	20.05

Alb SO4 = Albustol Sulfate

IPB = Ipratropium Bromide

SAR = Single Activation Reproducibility

Water Content (ppm)

Activation	Can 6	Can 7	Can 8	Can 9	Can 10
16-20	706	699	689	705	674
199-203	776	767	778	788	761

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7503

Theoretical Water Content: 1000ppm

Analyst: Brook White

Activation Number	Test	Inverted									
		Can 1		Can 2		Can 3		Can 4		Can 5	
25	Test	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
26	SAR	119.53	21.41	115.26	20.43	120.54	21.28	119.53	21.11	119.22	20.97
33	SAR	117.87	20.41	118.87	21.03	120.08	20.94	127.94	22.08	122.63	21.68
34	SAR	66.45	20.06	61.57	20.56	68.92	20.67	75.56	21.64	64.60	20.49
45-46	Dose	154.57	21.19	149.77	20.11	147.67	20.40	149.92	20.42	157.16	20.72
69	SAR	103.75	20.11	102.91	19.73	106.51	20.53	111.15	20.83	110.27	20.56
70	SAR	60.79	19.61	55.17	19.58	60.55	19.83	62.48	20.96	67.43	19.78
105-106	Dose	152.72	20.44	144.75	19.98	156.18	20.81	157.57	20.73	144.23	20.33
129	SAR	112.72	20.10	110.56	20.10	113.97	20.68	114.57	20.73	113.18	20.34
130	SAR	72.77 ²	20.19 ²	57.44	19.53	63.86	19.95	65.41	20.83	66.83	19.98
165-166	Dose	218.96 ²	51.20 ²	141.27	20.17	143.49	20.80	155.02	22.09	147.87	20.91
187	SAR	103.11	19.58	101.52	19.97	108.29	20.80	109.34	20.98	103.87	20.32
188	SAR	89.85	19.85	63.00	19.70	67.44	20.67	78.93	22.96	70.80	20.65
		135.42	21.69	138.18	20.71	140.29	21.73	143.79	21.50	145.14	22.12

Alb SO4 = Albument Sulfate

IPB = Ipratropium Bromide

SAR = Single Activation Reproducibility

Water Content (ppm)

Activation	Can 1	Can 2	Can 3	Can 4	Can 5
16-20	892	911	919	918	880
199-203	1019	995	1018	1033	983

¹ Data was obtained by rechallenge due to out of trend results for the second activation of this test. Results of 71.96 and 19.96 µg confirmed for Albument Sulfate and Ipratropium Bromide respectively.

² Data was confirmed by rechallenge since it was out of trend with the data set. Results of 214.59 and 49.91 µg were obtained for Albument Sulfate and Ipratropium Bromide respectively. Analytical error is suspected but could not be confirmed. The sponsor requested to report the data with no further investigation.

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7503

Theoretical Water Content: 1000ppm

Analyst: Nichole Byrum

Activation Number	Test	Upright									
		Can 6		Can 7		Can 8		Can 9		Can 10	
25	SAR	119.34	21.03	117.10	21.04	117.19	20.91	116.11	20.80	115.67	20.69
26	SAR	123.22	21.36	116.02	20.31	117.45	20.44	117.78	20.58	118.97	20.92
33	SAR	108.61	20.57	114.23	20.63	113.92	19.80	114.38	20.00	110.63	19.08
34	SAR	132.58	20.98	117.31	19.03	114.35	19.27	121.27	19.69	120.60	20.04
45-46	Dose	102.75	20.12	106.17	19.35	110.84	18.77	109.84	19.40	106.21	18.16
69	SAR	39.01	19.73	42.26	19.64	43.31	19.58	48.47	20.20	39.69	19.38
70	SAR	168.30	21.82	160.79	19.54	44.79	5.41 [*]	152.80	19.17	148.38	18.04
105-106	Dose	116.50	20.06	114.20	19.35	108.99	19.00	113.06	19.37	110.08	18.83
129	SAR	56.87	21.02	96.09	19.72	107.59	20.20	105.46	20.43	87.33	20.02
130	SAR	152.62	20.61	128.39	19.42	117.70	19.45	125.52	19.90	134.88	18.48
165-166	Dose	108.03	20.49	117.27	19.70	105.54	19.52	111.27	19.09	111.82	18.53
187	SAR	88.56	20.95	42.13	20.80	53.94	20.73	103.14	20.27	42.25	19.97
188	SAR	128.73	20.91	147.33	19.53	146.23	19.64	117.17	20.09	147.48	20.06

Ab SO4 = Albuterol Sulfate

IPB = Ipratropium Bromide

SAR = Single Activation Reproducibility

Water Content (ppm)

Activation	Can 6	Can 7	Can 8	Can 9	Can 10
16-20	936	909	886	915	909
199-203	1045	1018	1013	1020	998

^{*} This value was lower than expected. However, there was no follow-up investigation of this result. This result was presented to the sponsor. The sponsor had no additional comments.

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7504

Theoretical Water Content: 1200ppm

Analyst: Dan Miska

Activation Number	Test	Inverted									
		Can 1		Can 2		Can 3		Can 4		Can 5	
		AB SO4	IPB	AB SO4	IPB	AB SO4	IPB	AB SO4	IPB	AB SO4	IPB
25	SAR	116.12	20.93	116.98	20.70	117.61	20.87	116.53	20.71	115.57	20.60
26	SAR	116.88	20.19	117.37	20.54	117.99	20.42	117.06	20.56	117.26	20.44
33	SAR	115.67	20.64	120.17	20.28	117.21	20.08	116.66	20.77	117.19	23.65
34	SAR	117.83	20.07	114.54	20.87	118.94	20.22	120.28	20.56	115.64	20.19
45-46	Dose	111.40	19.73	112.34	26.72	109.13	19.19	113.77	20.06	114.25	19.97
69	SAR	83.73	20.12	100.71	19.82	86.07	20.13	88.78	21.01	94.15	19.54
70	SAR	138.10	20.16	123.70	20.33	139.96	20.57	131.06	19.38	132.44	20.56
105-106	Dose	111.05	19.45	110.63	19.63	112.42	19.86	110.90	19.74	110.94	19.75
129	SAR	81.29	19.86	80.29	19.96	88.14	20.50	82.38	19.87	88.28	20.43
130	Dose	136.53	19.87	138.94	20.34	140.03	20.22	139.48	20.73	145.92	21.22
165-166	SAR	107.59	19.89	107.69	19.87	108.52	19.97	108.39	20.14	110.74	20.19
187	SAR	113.81	20.29	118.65	20.79	102.22	21.08	97.04	20.54	101.05	20.69
188	SAR	117.03	20.89	111.13	20.59	120.00	20.58	127.32	21.03	117.76	20.01

AB SO4 = Albuterol Sulfate

IPB = Ipratropium Bromide

SAR = Single Activation Reproducibility

Water Content (ppm)

Activation	Can 1	Can 2	Can 3	Can 4	Can 5
16-20	1081	1102	1066	1064	1000
199-203	1168	1169	1155	1160	1099

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7504

Theoretical Water Content: 1200ppm

Analyst: Kathryn Johnson

Activation Number	Test	Upright									
		Can 6 Alb SO4	IPB	Can 7 Alb SO4	IPB	Can 8 Alb SO4	IPB	Can 9 Alb SO4	IPB	Can 10 Alb SO4	IPB
25	SAR	116.10	21.10	114.03	20.41	112.53	20.47	114.66	20.89	116.74	20.97
26	SAR	113.22	19.97	116.02	20.73	115.40	20.57	118.59	21.44	113.78	20.05
33	SAR	48.49	20.05	67.76	19.86	43.53	18.90	55.28	19.82	58.49	20.20
34	SAR	158.76	18.40	155.17	18.58	170.51	19.45	162.81	18.78	157.29	18.99
45-46	Dose	100.66	17.79	104.98	18.43	98.69	17.57	107.29	19.38	103.50	19.15
69	SAR	40.69	19.14	40.95	19.10	50.42	18.85	49.55	19.44	41.17	18.60
70	SAR	152.82	17.78	155.40	17.44	147.61	17.45	155.81	19.48	167.65	18.68
105-106	Dose	103.29	17.92	103.79	18.25	102.22	17.79	105.39	18.17	102.98	18.32
129	SAR	52.51	19.10	59.54	19.88	57.51	19.25	75.05	19.87	51.54	19.51
130	SAR	138.19	17.26	144.92	19.03	138.06	17.93	133.71	19.07	145.81	18.57
165-166	Dose	93.54	16.05	96.38	16.46	93.60	17.05	99.05	17.39	99.44	17.26
187	SAR	31.05	19.40	34.49	20.21	37.58	18.60	43.68	20.52	31.99	20.24
188	SAR	147.05	18.96	151.85	19.20	144.52	18.83	146.22	19.65	148.92	19.78

Alb SO4 = Albiterol Sulfate

IPB = Ipratropium Bromide

SAR = Single Activation Reproducibility

Water Content (ppm)					
Activation	Can 6	Can 7	Can 8	Can 9	Can 10
16-20	1063	1066	1060	1071	1082
199-203	1159	1173	1154	1175	1184

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7505

Theoretical Water Content: 1500ppm

Analyst: Brook White

Activation Number	Test	Inverted									
		Can 1		Can 2		Can 3		Can 4		Can 5	
25	SAR	AB SO4	IPB	AB SO4	IPB	AB SO4	IPB	AB SO4	IPB	AB SO4	IPB
26	SAR	116.21	20.67	113.96	20.74	119.88	21.38	126.79	22.26	118.66	21.10
33	SAR	118.46	20.67	116.09	20.10	121.20	21.20	122.00	21.34	116.72	20.73
34	SAR	112.55	19.84	116.28	20.82	114.67	20.34	113.06	20.31	114.61	20.86
45-46	Dose	117.06	20.80	111.72	19.32	118.41	20.54	110.90	19.19	115.39	20.39
69	SAR	110.45	19.80	111.29	19.78	114.27	20.55	112.32	19.91	113.49	20.17
70	SAR	99.24	19.26	108.44	20.24	99.74	20.02	105.97	20.25	101.45	20.17
105-106	Dose	122.24	20.06	119.12	20.08	124.01	20.35	118.92	19.94	124.88	20.31
129	SAR	111.73	20.21	113.12	20.06	113.20	20.48	112.03	19.96	114.97	20.84
130	SAR	113.98	20.14	113.93	19.94	112.79	20.78	110.89	20.07	108.77	19.69
165-166	Dose	118.36	21.38	115.40	20.20	116.83	20.81	115.00	20.45	125.57	22.64
187	SAR	107.47	19.95	112.14	20.24	110.44	20.25	109.26	20.24	109.89	20.29
188	SAR	117.19	20.72	119.51	20.61	110.54	20.51	107.43	20.37	119.79	20.74
		107.92	20.35	114.33	20.87	122.09	22.64	112.39	21.22	117.01	22.25

AB SO4 = Alburel Sulfate

IPB = Ipratropium Bromide

SAR = Single Activation Reproducibility

Water Content (ppm)

Activation	Can 1	Can 2	Can 3	Can 4	Can 5
16-20	1381	1430	1361	1413	1380
199-203	1488	1488	1488	1503	1486

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7505

Theoretical Water Content: 1500ppm

Analyst: Nichole Bynum

Actuation Number	Test	Upright									
		Can 6		Can 7		Can 8		Can 9		Can 10	
25	SAR	Ab SO4	IPB	Ab SO4	IPB	Ab SO4	IPB	Ab SO4	IPB	Ab SO4	IPB
26	SAR	116.73	20.84	117.75	20.66	119.88	20.65	117.66	20.83	125.01	21.96
33	SAR	113.69	20.06	115.37	20.18	118.13	20.57	125.89	21.77	124.74	21.81
34	SAR	119.64	22.47	116.18	19.72	118.66	20.09	119.61	20.44	116.61	20.40
45-46	Dose	119.72	19.94	117.46	19.94	118.13	19.56	119.28	19.61	121.44	20.13
69	SAR	114.78	19.30	114.70	19.16	108.98	18.65	114.77	19.74	112.26	18.47
70	SAR	112.18	20.14	116.05	19.46	111.65	19.43	114.12	20.20	114.19	19.60
105-106	Dose	122.24	20.85	117.55	19.33	110.99	18.25	118.92	20.47	118.45	18.81
129	SAR	116.16	19.95	114.83	19.56	112.33	19.05	112.30	20.42	114.25	19.85
130	SAR	113.66	20.70	109.67	19.65	122.59	19.86	116.34	20.45	112.39	19.84
165-166	Dose	113.45	20.18	121.31	19.92	85.89	14.92	112.48	19.30	121.42	20.02
187	SAR	109.10	20.13	108.94	19.64	114.02	18.91	110.36	20.11	115.55	17.60
188	SAR	97.28	20.74	99.90	19.93	105.47	20.31	107.48	20.96	104.49	20.53
		126.94	21.01	116.29	19.90	111.20	19.25	111.98	20.10	110.54	20.38

Ab SO4 = Albuterol Sulfate

IPB = Ipratropium Bromide

SAR = Single Actuation Reproducibility

Water Content (ppm)

Actuation:	Can 6	Can 7	Can 8	Can 9	Can 10
16-20	1367	1397	1369	1428	1381
199-203	1491	1492	1471	1562	1498

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7506

Theoretical Water Content: 2500ppm

Analyst: Dan Mita

Activation Number	Test	Inverted									
		Can 1		Can 2		Can 3		Can 4		Can 5	
		Ab SO4	IPB	Ab SO4	IPB	Ab SO4	IPB	Ab SO4	IPB	Ab SO4	IPB
25	SAR	122.31	20.76	124.13	21.38	119.40	20.64	119.42	20.36	119.08	20.20
26	SAR	113.19	20.34	116.23	20.70	116.41	20.91	112.91	20.41	114.47	20.75
33	SAR	119.83	20.11	122.52	21.04	118.66	20.20	117.66	20.03	116.36	20.63
34	SAR	111.77	20.44	115.00	20.33	116.30	21.09	111.81	20.13	111.95	20.63
45-46	Dose	113.79	19.84	115.73	20.62	114.49	20.17	110.62	19.64	111.29	20.07
69	SAR	116.56	19.06	122.37	20.74	120.39	20.43	117.88	20.32	120.73	20.49
70	SAR	114.39	20.46	112.99	20.27	112.45	20.60	111.14	19.64	108.17	20.23
105-106	Dose	115.43	20.35	117.74	20.53	115.95	20.43	114.04	19.91	112.84	19.81
129	SAR	118.77	20.26	119.46	20.71	118.05	20.49	116.71	19.78	118.50	20.18
130	SAR	117.04	21.16	113.68	21.26	115.08	21.15	108.10	20.10	108.95	20.17
165-166	Dose	109.04	20.06	111.09	20.55	108.86	19.84	107.36	19.43	106.84	19.87
187	SAR	112.35	20.52	114.37	20.90	113.56	20.83	112.29	20.10	113.38	20.71
188	SAR	109.54	20.86	112.00	21.27	110.88	21.09	106.57	20.69	106.19	21.48

Ab SO4 = Albuterol Sulfate

IPB = Ipratropium Bromide

SAR = Single Activation Reproducibility

Water Content (ppm)

Activation	Can 1	Can 2	Can 3	Can 4	Can 5
16-20	2368	2372	2336	2313	2370
199-203	2502	2483	2466	2479	2465

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7556

Theoretical Water Content: 2500ppm

Analyst: Kathryn Johnson

Activation Number	Test	Upright									
		Can 6		Can 7		Can 8		Can 9		Can 10	
25	Test	Ab SO4	IPB	Ab SO4	IPB	Ab SO4	IPB	Ab SO4	IPB	Ab SO4	IPB
26	SAR	118.31	20.22	121.52	20.71	122.54	21.01	120.44	21.14	119.51	20.58
33	SAR	116.30	21.63	115.59	21.24	115.78	20.96	115.26	21.33	118.52	21.78
34	SAR	118.15	19.67	123.20	20.24	108.74	18.68	112.74	18.66	116.39	19.08
45-46	Dose	110.16	19.68	111.55	19.23	123.30	19.05	118.92	19.67	112.31	18.76
69	SAR	108.85	19.69	115.19	20.10	109.42	18.35	110.01	18.79	112.51	19.01
70	SAR	114.10	19.92	116.72	20.56	109.25	19.37	110.22	18.85	112.76	20.10
105-106	Dose	108.20	18.66	109.74	18.78	108.62	17.54	110.10	18.58	106.14	19.68
129	SAR	103.46	18.53	106.70	19.25	103.64	18.18	104.61	18.86	102.27	18.19
130	SAR	105.51	19.90	106.09	19.84	104.55	19.93	105.78	19.51	107.21	19.65
165-166	Dose	104.97	19.09	106.68	19.73	111.66	18.76	106.94	19.75	108.97	19.96
187	SAR	95.47	18.82	99.41	19.17	96.08	17.94	98.80	19.22	94.20	18.74
188	SAR	100.26	21.00	101.76	20.59	97.34	20.18	98.89	20.03	93.45	20.01
		95.69	20.01	95.40	20.51	102.57	18.92	97.96	20.08	92.92	19.25

Ab SO4 = Alburel Sulfate

IPB = Ipratropium Bromide

SAR = Single Activation Reproducibility

Water Content (ppm)

Activation	Can 6	Can 7	Can 8	Can 9	Can 10
16-20	2362	2356	2327	2306	2246
199-203	2473	2499	2456	2460	2488

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7507

Theoretical Water Content: 3000ppm

Analyst: Brook White

Activation Number	Test	Inverted									
		Can 1		Can 2		Can 3		Can 4		Can 5	
25	SAR	Ab SO4	IPB	Ab SO4	IPB	Ab SO4	IPB	Ab SO4	IPB	Ab SO4	IPB
26	SAR	116.79	20.63	118.78	20.84	114.65	19.88	115.17	20.26	114.81	20.36
33	SAR	116.64	20.34	114.57	20.24	113.22	20.02	117.60	21.12	114.75	20.95
34	SAR	116.12	20.18	114.51	19.30	111.95	19.23	116.47	20.44	114.74	20.23
45-46	Dose	115.87	20.62	113.18	19.59	109.45	19.21	113.72	20.14	112.13	19.84
69	SAR	113.55	20.27	111.76	19.86	110.04	19.66	112.80	20.11	110.32	19.90
70	SAR	109.91	19.33	114.65	20.07	109.43	18.77	114.66	19.86	113.59	20.15
105-106	Dose	110.79	20.15	111.36	19.66	108.25	19.50	108.31	19.41	112.30	19.95
129	SAR	106.24	19.04	105.50	18.97	104.43	18.94	108.74	19.65	105.61	19.64
139	SAR	111.53	19.66	112.73	20.08	108.28	19.59	112.30	19.79	111.44	19.67
151	SAR	111.51	20.43	112.78	20.33	107.66	19.59	110.29	20.15	111.13	20.54
165-166	Dose	104.08	19.03	105.03	19.81	102.79	19.27	106.09	20.13	101.12	19.55
187	SAR	105.30	19.64	106.67	20.02	105.85	19.30	108.70	20.34	104.53	20.37
188	SAR	108.80	21.15	105.98	20.34	102.38	20.16	109.39	21.92	106.77	21.39

Ab SO4 = Albuterol Sulfate

IPB = Ipratropium Bromide

SAR = Single Activation Reproducibility

Water Content (ppm)

Activation	Can 1	Can 2	Can 3	Can 4	Can 5
16-30	2880	2897	2847	2812	3071
199-203	3072	3059	3016	3040	3304

Uniformity of Dose Water Challenge

Results reported in µg recovered

Location:

AS Number: 02-10-7507

Theoretical Water Content: 3000ppm

Analyst: Kathryn Johnson

Actuation Number	Test	Upright									
		Can 6		Can 7		Can 8		Can 9		Can 10	
		Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
25	SAR	115.63	20.16	113.86	19.80	116.54	20.24	112.98	19.99	115.98	20.94
26	SAR	107.23	19.69	107.73	19.16	115.99	20.91	111.69	20.12	111.83	20.05
33	SAR	115.88	19.98	114.25	19.05	114.43	19.24	113.75	18.92	114.69	19.39
34	SAR	105.62	17.80	108.54	17.95	114.01	18.69	112.02	18.30	111.47	18.97
45-46	Dose	105.31	17.63	104.60	17.76	109.46	18.27	105.77	17.84	104.59	17.82
69	SAR	101.08	19.01	106.33	18.83	107.76	19.42	108.06	19.17	107.30	19.12
70	SAR	108.12	17.37	106.76	17.85	113.24 ¹	18.66 ¹	108.54	19.06	104.75	18.35
105-106	Dose	101.02	17.35	102.02	18.07	103.96	17.68	102.51	18.06	101.53	18.08
129	SAR	103.08	19.77	103.14	18.08	102.88	19.45	108.60	19.57	104.96	19.51
139	SAR	106.76	17.27	108.04	18.54	115.61	19.45	102.71	18.65	103.97	18.55
165-166	Dose	90.88	12.85	70.26	8.52	87.87	10.13	89.64	12.38	89.04	13.95
187	SAR	96.45	19.42	90.68	19.05	87.57	19.62	87.02	19.59	86.35	19.42
188	SAR	88.82	18.99	90.26	18.84	100.53	20.92	91.29	19.42	80.36	19.44

Alb SO4 = Albendazole Sulfate

IPB = Iprazurium Bromide

SAR = Single Actuation Reproducibility

Water Content (ppm)

Actuation	Can 6	Can 7	Can 8	Can 9	Can 10
16-20	2795	2855	2831	2805	2841
199-203	2956	3049	3004	2976	3008

¹Analyst observed that this actuation sounded weaker than normal.

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7508

Theoretical Water Content: 3500ppm

Analyst: Brook White

Activation Number	Test	Inverted									
		Can 1		Can 2		Can 3		Can 4		Can 5	
25	SAR	AB SQ4	IPB	AB SQ4	IPB	AB SQ4	IPB	AB SQ4	IPB	AB SQ4	IPB
26	SAR	119.26	21.31	114.26	20.00	113.72	20.20	109.36	19.76	111.65	19.84
33	SAR	116.90	20.55	104.49	19.16	108.69	19.55	115.32	20.69	112.33	19.77
34	SAR	109.74	19.54	115.38	20.34	110.26	19.76	111.04	19.22	114.81	20.06
45-46	Dose	114.78	20.24	109.11	20.00	110.68	19.26	113.07	20.00	114.46	20.74
69	SAR	108.77	19.61	106.58	19.62	106.91	19.52	108.66	20.02	108.71	19.72
70	SAR	110.29	19.31	111.13	20.05	105.45	19.29	108.26	19.49	110.86	19.65
105-106	Dose	102.54	18.78	109.88	19.94	108.21	20.05	108.26	20.34	113.82	20.50
129	SAR	112.03	20.40	108.01	19.88	107.55	20.08	105.69	19.45	109.58	20.01
130	SAR	110.87	20.93	109.67	20.58	108.77	20.84	108.23	19.97	106.11	19.70
165-166	Dose	101.92	19.77	98.75	19.31	97.24	18.46	100.21	19.81	100.89	19.01
187	SAR	102.85	20.05	104.49	20.09	106.31	20.19	99.75	19.07	105.50	19.50
188	SAR	104.69	21.04	99.83	20.07	103.75	21.25	101.51	21.24	99.90	20.34

AB SQ4 = Albuterol Sulfate

IPB = Ipratropium Bromide

SAR = Single Activation Reproducibility

Water Content (ppm)

Activations	Can 1	Can 2	Can 3	Can 4	Can 5
16-20	3416	3352	3367	3320	3302
199-203	3533	3556	3558	3540	3551

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7308

Theoretical Water Content: 3500ppm

Analyst: Kathryn Johnson

Activation Number	Test	Upright									
		Can 6		Can 7		Can 8		Can 9 ¹		Can 10	
25	Test	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
26	SAR	112.02	20.13	114.41	19.95	115.22	19.99	117.50	20.48	116.70	20.62
33	SAR	108.44	19.80	114.58	21.22	109.67	20.27	109.60	20.23	107.58	19.57
34	SAR	109.10	18.51	109.33	18.95	117.84	20.51	112.49	18.89	110.15	19.19
45-46	Dose	110.44	18.09	100.80	19.74	106.24	19.27	111.46	18.80	116.55	18.97
69	SAR	105.40	18.21	99.55	17.22	109.08	19.31	106.55	17.97	108.31	18.30
70	SAR	101.42	18.38	102.63	18.04	104.06	18.76	104.88	17.15	103.54	19.23
105-106	Dose	101.56	18.03	101.28	17.68	105.87	18.39	103.37	17.85	104.14	17.96
129	SAR	96.51	19.09	98.10	17.45	101.57	18.96	99.14	18.12	103.08	19.85
130	SAR	106.27	18.43	98.85	17.92	112.53	19.76	101.08	19.14	107.76	18.90
165-166	Dose	88.29	12.23	85.45	11.54	92.06	13.77	91.10	13.67	92.48	14.08
187	SAR	90.87	19.18	94.74	19.23	98.05	19.83	87.74	19.18	91.15	20.00
188	SAR	84.44	19.42	85.29	19.97	86.82	19.65	81.18	19.60	83.01	19.58

Alb SO4 = Albuteol Sulfate

IPB = Ipratropium Bromide

SAR = Single Activation Reproducibility

Water Content (ppm)

Activations	Can 6	Can 7	Can 8	Can 9 ¹	Can 10
16-20	3360	3381	3404	3396	3365
199-203	3528	3360	3572	3567	3551

¹During initial water content testing, 6 activations may have been made (16-21 activations). Sponsor was notified.

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7509

Theoretical Water Content: 4000ppm

Analyst: Brook White

Activation Number	Test	Inverted									
		Can 1		Can 2		Can 3		Can 4		Can 5	
		Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
25	SAR	111.00	20.05	111.12	20.08	107.69	19.85	109.37	19.78	109.53	20.26
26	SAR	114.93	19.82	108.69	19.84	105.13	19.80	111.82	20.29	109.57	20.61
33	SAR	111.64	19.64	108.50	19.29	107.54	19.66	109.40	19.63	112.92	20.30
34	SAR	108.96	19.71	103.73	19.06	103.49	19.75	110.56	19.85	109.26	20.35
45-46	Dose	105.70	19.34	107.09	19.33	103.04	18.84	107.71	19.52	108.75	20.05
69	SAR	107.67	19.19	108.24	19.42	103.84	19.33	103.61	19.28	109.93	19.81
70	SAR	110.99	19.80	106.52	20.27	100.93	18.86	109.04	20.61	107.58	20.24
105-106	Dose	103.56	18.83	102.73	19.31	101.74	19.22	104.33	19.37	107.92	19.91
129	SAR	108.69	19.43	106.55	19.37	103.40	19.04	106.54	20.05	110.48	20.40
139	SAR	105.58	20.83	105.30	20.37	97.61	18.90	102.24	19.86	107.98	20.88
165-166	Dose	93.00	18.04	95.39	19.28	91.81	18.85	95.40	19.48	99.05	19.48
187	SAR	95.14	20.18	96.00	19.67	97.45	19.73	98.47	19.44	97.47	19.54
188	SAR	94.35	20.32	93.34	20.10	95.22	20.11	96.11	21.03	99.88	21.63

Alb SO4 = Alburexol Sulfate

IPB = Ipratropium Bromide

SAR = Single Activation Reproducibility

Water Content (ppm)

Activation	Can 1	Can 2	Can 3	Can 4	Can 5
16-30	3805	3822	3843	3754	3811
199-203	4045	4003	4033	3938	4014

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7309

Theoretical Water Content: 4000ppm

Analyst: Kathryn Johnson

Actuation Number	Test	Upright									
		Can 6		Can 7		Can 8		Can 9		Can 10	
		Abt SO4	IPB	Abt SO4	IPB	Abt SO4	IPB	Abt SO4	IPB	Abt SO4	IPB
25	SAR	116.70	20.77	110.63	19.79	109.67	19.99	108.48	19.93	113.94	20.11
26	SAR	110.22	20.49	110.25	20.45	108.48	20.01	110.55	20.52	107.93	20.42
33	SAR	104.40	18.46	107.39	18.49	101.89	18.89	99.49	18.78	101.71	18.83
34	SAR	112.67	17.93	112.71	17.96	113.58	17.39	110.43	17.55	109.57	17.68
45-46	Dose	107.88	18.44	104.94	17.04	103.43	17.40	102.29	17.56	101.34	17.57
69	SAR	98.58	19.10	91.55	15.39	95.34	17.19	92.18	16.41	95.75	16.97
79	SAR	118.85	18.97	117.62	19.28	116.26	18.73	110.24	18.37	113.12	18.90
105-106	Dose	105.70	18.66	96.35	15.50	97.83	15.05	95.71	15.62	97.11	16.02
129	SAR	99.24	19.76	93.70	18.79	94.21	18.95	88.04	18.29	94.86	18.32
130	SAR	106.17	18.91	109.41	18.80	107.94	19.14	108.32	19.36	107.04	19.00
165-166	Dose	80.34	10.28	87.96	12.20	91.87	14.17	85.30	13.57	87.78	12.70
187	SAR	81.95	19.26	73.03	17.19	76.95	17.66	75.68	19.32	80.47	18.37
188	SAR	74.83	19.48	85.99	18.39	87.35	19.29	66.70	18.68	89.32	20.28

Abt SO4 = Abturod Sulfate

IPB = Ipratropium Bromide

SAR = Single Actuation Reproducibility

Water Content (ppm)

Actuation	Can 6	Can 7	Can 8	Can 9	Can 10
16-20	3815	3741	3760	3829	3708
199-203	3995	3963	3958 ¹	4000	3925

¹This canister was inadvertently tested at actuations 200-204.

I. Purpose

The purpose of this study is to examine the effects of water content in Ipratropium Bromide/Albuterol Sulfate 0.021/0.120 mg TTV, 10 mL Inhalation Aerosol on testing for Single Actuation and Dose (2 actuations) through life (ca. 200 actuations).

II. Applicable Regulatory Requirements

This study will be conducted as per GMP (21 CFR 210 and 211) regulations.

III. Materials

BIP1 will manufacture canisters using the same formulation but different water contents. The samples will be grouped as follows.

AS Testing Number	Lot Number	Target ppm Water
02-10-7501	A1	Inherent*
02-10-7502	A2	800*
02-10-7503	A3	1000*
02-10-7504	A4	1200*
02-10-7505	A5	1500*
02-10-7506	A6	2500*
02-10-7507	A7	3000
02-10-7508	A8	3500
02-10-7509	B8	4000

IV. Study Design

A total of 90 canisters will be tested utilizing the following table. Ten (10) canisters will be selected from each lot, Five (5) to be stored in an upright orientation and Five (5) in an inverted orientation. Canisters will be placed in orientation immediately following initial Water Content testing and will be stored and weighed in their designated orientation throughout the study life.

Water Content testing will be performed at the beginning and end of the study per the following table. Initial Water Content testing will occur no earlier than the Friday prior initiation of the testing schedule. If the initial Water Content is performed on the preceding Friday, then conduct testing as indicated for Beginning Testing Option 1. Otherwise, proceed as indicated in Beginning Testing Option 2.

* Priority sample, test before other samples.

Final Water Content testing may occur as late as the Monday following the end of the study, if necessary. No change to the testing scheme below will be needed if testing is delayed for final Water Content.

For all methods, calculate sample weights as follows: $W1 - W2 = \text{Sample Weight}$
 W2 is the canister weight recorded immediately following each test point and W1 is the canister weight prior to testing (previous timepoint's W2.)

Wasting actuations will be performed using a jar and baseplate. A delay of no less than 2 hours must occur between completion of previous wasting timepoint and initiation of next wasting timepoint when multiple wasting sessions are required on the same day. The firing and shaking of canisters is to be performed as outlined in the Uniformity of Dose procedure for wasting canisters. A swab will be used to thoroughly clean the interior of the valve stem prior to collecting the final weight for both the Water Content and the Wasting steps. It is critical to clean the valve stem while the interior is still wet from the testing step. Wasting will be performed per the following table.

Samples must equilibrate for 24 hours before any Uniformity of Dose sampling can be performed. The single actuation reproducibility protocol (SAR) requires that two single actuations be collected in separate containers where indicated. Do not shake canisters between actuations for the SAR protocol. Uniformity of Dose samples will be collected per the following table.

Record testing times as follows:

Water Content testing: It is not necessary to record testing times.

Uniformity of Dose/SAR testing: Record time testing was initiated.

Wasting: Record the time testing was initiated and completed.

Beginning Testing Option 1: Water Content testing performed on preceding Friday

Week 1		
Day	Actuation Number	Action
Preceding Friday	1-5	Priming
	6-15	Clearing the Inlet Tube (Water Content)
	16-20	Water Content Sample
Monday	21-24	Priming
	25 & 26	0 hr SAR
	27-32	Shot weight collection
		Actuate to waste after 0 hr SAR
		Shot weight collection

Then continue with testing as indicated below for Week 1 Tuesday.

Beginning Testing Option 2: Water Content testing performed on preceding Friday

Week 1		
Day	Actuation Number	Action
Monday	1-5 [*]	Priming
	6-15 [*]	Clearing the Inlet Tube (Water Content)
	16-20 [*]	Water Content Sample
	21 & 22	0 hr SAR Shot weight collection
	23-32	Actuate to waste after 0 hr SAR Shot weight collection

Then continue with testing as indicated below for Week 1 Tuesday.

Week 1		
Day	Actuation Number	Action
Tuesday	33 & 34 ^{**}	24 hr SAR Shot weight collection
	35-44	Actuate to waste after 24 hr SAR Shot weight collection
Wednesday	45-46 ^{**}	24 hr Dose Shot weight collection
	47-48	Actuate to waste after Dose Shot weight collection
	49-52	Actuate to waste Mid Day Shot weight collection
	53-56	Actuate to waste End Day Shot weight collection
Thursday	57-68	Actuate to waste Shot weight collection
Friday	69 & 70 ^{**}	24 hr SAR Shot weight collection
	71-72	Actuate to waste after 24 hr SAR (actuators 69 & 70) Shot weight collection
	73-76	Actuate to waste Mid Day Shot weight collection
	77-80	Actuate to waste End Day Shot weight collection

^{*} May be performed as early as the Friday prior.

^{**} Must occur at least 24 hours from completion of prior wasting timepoint.

Week 2		
Day	Actuation Number	Action
Monday	81-84	Actuate to waste Beg Day Shot weight collection
	85-88	Actuate to waste Mid Day Shot weight collection
	89-92	Actuate to waste End Day Shot weight collection
Tuesday	93-104	Actuate to waste Shot weight collection
Wednesday	105-106**	24 hr Dose Shot weight collection
	107-108	Actuate to waste after 24 hr Dose (actuators 105 & 106) Shot weight collection
	109-112	Actuate to waste Mid Day Shot weight collection
	113-116	Actuate to waste End Day Shot weight collection
Thursday	117-128	Actuate to waste Shot weight collection
Friday	129 & 130**	24 hr SAR Shot weight collection
	131-132	Actuate to waste after 24 hr SAR (actuators 129 & 130) Shot weight collection
	133-136	Actuate to waste Mid Day Shot weight collection
	137-140	Actuate to waste End Day Shot weight collection

** Must occur at least 24 hours from completion of prior wasting timepoint.

Week 3		
Day	Actuation Number	Action
Monday	141-144	Actuate to waste Beg Day Shot weight collection
	145-148	Actuate to waste Mid Day Shot weight collection
	149-152	Actuate to waste End Day Shot weight collection
Tuesday	153-164	Actuate to waste Shot weight collection
Wednesday	165-166**	24 hr Dose Shot weight collection
	167-168	Actuate to waste after 24 hr Dose (actuators 165 & 166) Shot weight collection
	169-172	Actuate to waste Mid Day Shot weight collection
	173-174	Actuate to waste End Day Shot weight collection
Thursday	175-186	Actuate to waste Shot weight collection
Friday	187 & 188**	24 hr SAR Shot weight collection
	189-198 *	Clear sample inlet tube (Water Content)
	199-203 *	Water Content Sample

V. Test Methods

Method	ATM #	BIPI TP #	Method Transfer
Water	ATM-:		TTP-
Uniformity of Dose	ATM-:		TTP-

VI. Reporting

Report the data using the Access Database provided in a Certificate of Analysis format. An electronic copy of the data should also be provided.

VII. Attachments

None.

* May be performed as late as the Monday following the last SAR.

** Must occur at least 24 hours from completion of prior wasting timepoint.

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7301

Theoretical Water Content: Inherent

Analyst: Brook White

Actuation Number	Test	Inverted									
		Can 1		Can 2		Can 3		Can 4		Can 5	
25	SAR	115.13	20.56	118.21	20.85	115.17	20.64	117.57	20.63	122.36	21.72
26	SAR	117.42	19.74	112.10	19.45	117.79	20.54	117.26	20.34	119.82	21.42
33	SAR	77.03	19.66	66.59	19.61	90.17	19.95	62.84	19.43	82.38	19.42
34	SAR	245.57	20.14	202.70	19.47	216.22	19.59	238.14	21.24	214.94	20.25
45-46	Dose	159.74	19.46	139.27	18.83	144.63	19.52	169.23	19.22	149.47	19.76
69	SAR	60.95	19.29	75.53	19.87	76.67	19.34	70.93	18.94	128.19	18.60
70	SAR	240.53	20.28	237.87	19.34	256.88	20.88	232.40	20.84	222.82	21.00
105-106	Dose	133.76	19.27	95.46	19.54	95.94	20.03	92.92	19.78	95.99	19.87
129	SAR	160.42 ¹	19.62 ¹	57.22	19.31	79.18	19.93	69.29	18.84	56.62	18.79
130	SAR	161.63 ²	19.62 ²	181.90	19.69	156.13	20.43	177.50	20.78	161.25	19.90
165-166	Dose	103.76	19.55	101.53	19.61	104.51	20.45	100.96	19.96	92.65	19.65
187	SAR	87.58	19.52	58.20	25.05	47.18	19.52	57.62	19.52	92.57	19.22
188	SAR	146.99	20.16	168.57	20.82	142.08	21.13	153.97	20.93	136.70	20.66

AB SO4 = Albuterol Sulfate

IPB = Ipratropium Bromide

SAR = Single Actuation Reproducibility

Water Content (ppm)

Actuation	Can 1	Can 2	Can 3	Can 4	Can 5
16-20	263	257	260	262	265
199-203	364	343	343	331	325

These values were confirmed by re-injection since they were not in trend with the data set. The re-injected samples yielded results of 167.16 and 18.81 µg for Albuterol Sulfate and Ipratropium Bromide respectively.

These values were confirmed by re-injection since they were not in trend with the data set. The re-injected samples yielded results of 160.32 and 19.42 µg for Albuterol Sulfate and Ipratropium Bromide respectively.

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7501

Theoretical Water Content: Inherent

Analyst: Nichole Byrum

Actuation Number	Test	Upright									
		Can 6	Can 6	Can 7	Can 7	Can 8	Can 8	Can 9	Can 9	Can 10	Can 10
25	Test	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
26	SAR	114.77	20.55	121.29	21.97	121.85	21.73	115.94	20.69	121.53	21.52
33	SAR	119.57	20.87	118.26	20.88	117.92	22.26	121.20	21.46	119.29	21.36
34	SAR	39.60	19.58	47.68	20.48	42.23	20.70	40.38	20.39	47.37	20.29
45-46	Dose	164.26	19.83	155.10	19.75	156.82	19.18	169.58	19.66	156.61	19.84
69	SAR	98.77	19.56	99.56	19.83	99.49	20.45	104.71	20.18	98.57	20.05
70	SAR	46.50	19.64	50.50	19.16	41.45	19.82	50.31	20.04	52.55	20.33
105-106	Dose	155.93	19.89	157.65	20.68	159.42	19.32	150.98	18.73	158.94	20.84
129	SAR	85.03	18.82	96.15	20.00	94.30	19.39	92.94	19.42	106.61	20.44
130	SAR	51.96	20.29	55.25	20.24	77.68	20.06	89.13	61.90	78.36	17.70
165-166	Dose	150.76	20.17	141.95	19.57	142.01	19.74	130.40	18.61	136.65	20.80
187	SAR	94.23	19.57	102.94 ²	17.66 ²	101.73	18.17	99.60 ²	16.83 ²	98.36 ²	16.97 ²
188	SAR	48.15	20.44	60.41	20.65	42.98	20.22	46.04	20.68	60.89	22.05
		149.23	20.66	140.19	20.92	150.85	21.02	152.92	20.66	138.40	21.78

Alb SO4 = Alburex Sulfate

IPB = Ipratropium Bromide

SAR = Single Actuation Reproducibility

Water Content (ppm)

Actuation	Can 6	Can 7	Can 8	Can 9	Can 10
16-20	275	270	260	268	279
199-203	341	337	327	330	402 ¹

¹The analyst observed an unusually weak plume for all 5 actuations.

²The analyst observed that the first actuation sounded weaker than normal.

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7305

Theoretical Water Content: 1500ppm

Analyst: Brook White

Activation Number	Test	Inverted									
		Can 1		Can 2		Can 3		Can 4		Can 5	
25	Test	Ab SO4	IPB	Ab SO4	IPB	Ab SO4	IPB	Ab SO4	IPB	Ab SO4	IPB
26	SAR	116.21	20.67	115.98	20.74	119.88	21.38	126.79	22.26	118.66	21.10
33	SAR	118.46	20.67	116.09	20.10	121.20	21.20	122.00	21.34	116.72	20.73
34	SAR	112.55	19.84	116.28	20.82	114.67	20.34	113.06	20.31	114.61	20.86
45-46	Dose	117.06	20.50	111.72	19.32	118.41	20.54	110.90	19.19	115.39	20.39
69	SAR	110.45	19.80	111.29	19.78	114.27	20.55	112.32	19.91	113.49	20.17
70	SAR	99.24	19.26	108.44	20.24	99.74	20.02	105.97	20.25	101.45	20.17
105-106	Dose	122.24	20.06	119.12	20.08	124.01	20.35	118.92	19.94	124.88	20.31
129	SAR	113.98	20.14	113.93	19.94	112.79	20.78	110.89	20.07	108.77	19.69
130	SAR	118.36	21.38	115.40	20.20	116.83	20.81	115.00	20.45	125.57	22.64
165-166	Dose	107.47	19.95	112.14	20.24	110.44	20.25	109.26	20.24	109.89	20.29
187	SAR	117.19	20.72	119.51	20.61	110.54	20.51	107.43	20.37	119.79	20.74
188	SAR	107.92	20.35	114.33	20.87	122.09	22.64	112.39	21.22	117.01	22.25

Ab SO4 = Albustrol Sulfate

IPB = Ipratroium Bromide

SAR = Single Activation Reproducibility

Water Content (ppm)

Activation	Can 1	Can 2	Can 3	Can 4	Can 5
16-20	1381	1430	1361	1413	1380
199-203	1488	1488	1438	1503	1486

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number: 02-10-7505

AS Number: 02-10-7505

Theoretical Water Content: 1500ppm

Analyst: Nichole Bryant

Activation Number	Test	Upright									
		Can 6		Can 7		Can 8		Can 9		Can 10	
25	SAR	AB SO4	IPB	AB SO4	IPB	AB SO4	IPB	AB SO4	IPB	AB SO4	IPB
26	SAR	116.73	20.84	117.75	20.66	119.88	20.65	117.66	20.83	125.01	21.96
33	SAR	113.69	20.06	115.37	20.18	118.13	20.57	125.89	21.77	124.74	21.81
34	SAR	119.64	22.47	116.18	19.72	118.66	20.09	119.61	20.44	116.61	20.40
45-46	Dose	119.72	19.94	117.46	19.94	118.13	19.56	119.28	19.61	121.44	20.13
69	SAR	114.78	19.30	114.70	19.16	108.98	18.65	114.77	19.74	112.26	18.47
70	SAR	112.18	20.14	116.05	19.46	111.63	19.43	114.12	20.20	114.19	19.60
105-106	Dose	122.24	20.65	117.55	19.33	110.99	18.25	118.92	20.47	118.45	18.81
129	SAR	116.16	19.95	114.83	19.56	112.33	19.05	112.30	20.42	114.25	19.85
130	SAR	113.46	20.70	109.67	19.65	122.59	19.86	116.34	20.45	112.39	19.84
165-166	Dose	113.46	20.18	121.31	19.92	109.40	18.51	112.48	19.30	121.42	20.02
187	SAR	109.10	20.13	108.94	19.64	114.02	18.91	110.36	20.11	115.55	17.60
188	SAR	97.28	20.74	99.50	19.93	105.47	20.31	107.48	20.96	104.49	20.53
		126.94	21.01	116.29	19.90	111.20	19.25	111.98	20.10	110.54	20.38

AB SO4 = Abated Sulfate

IPB = Ipratroprum Bromide

SAR = Single Activation Reproducibility

Water Content (ppm)

Activation	Can 6	Can 7	Can 8	Can 9	Can 10
16-20	1367	1395	1369	1428	1381
199-203	1491	1492	1471	1562	1498



**Boehringer
Ingelheim**

ANALYTICAL SCIENCES DEPARTMENT

ANALYTICAL REPORT

Title: Results for In Use 6 Hour Delay Single Actuation Reproducibility Study for Ipratropium Bromide/Albuterol Sulfate Inhalation Aerosol, with Water Contents Ranging from Inherent Water to 2500 ppm

Author(s): Johanna Ubben

Date of Report: 05 Feb 2003

Product / Project:

Project Code: BP

Requester: George DeStefano

cc: P. D. Curry, Jr, Ph.D.; E. Gump, Ph.D.; R. Patel, Ph.D.

Sample ID: 02-10-7515, 02-10-7516, 02-10-7517, 02-10-7518, 02-10,7519, 02-10-7520

Key Words: Combivent HFA, dose uniformity, water content, single actuation reproducibility, valve delivery through life, total can assay

File Number: AR-030012

Security: Read Only

Signature: *Johanna Ubben* Feb 21, 2003

Verification: *[Signature]* Feb. 21, 2003

Data Reference(s): 5886/083

I. Introduction

Samples from Ipratropium Bromide/Albuterol Sulfate Inhalation Aerosol, Lot: were submitted to the Pulmonary Analysis Laboratory for a patient in-use, single actuation reproducibility study. The protocol detailing the experimental plan for this study is shown in Attachment 1. The purpose of this report is to summarize the results of this testing

II. Samples

All samples used the Bespak Valve #BK0080332, 0.05% PVP, and 10 % ethanol.

- A1 – Inherent Water
- A2 – 800 ppm Water
- A3 – 1000 ppm Water
- A4 – 1200 ppm Water
- A5 – 1500 ppm Water
- A6 – 2500 ppm Water

III. Test Procedures

- TP-4 Water Content
- TP-4 Dose Uniformity (US)
- TP-4 Total Can Assay

Single Actuation Reproducibility – Experimental Procedure described in protocol

TP-4, Valve Delivery Through Life – with modification described in protocol

Orientation	Canister Number	Beginning of Study (ppm)	End of Study (ppm)
Inverted	3	1388.0	1459.0
Inverted	4	1383.0	1612.0
Inverted	5	1375.0	1597.0
Upright	1	2724.0	1799.0
Upright	2	4774.0	1767.0
Upright	3	2347.0	1791.0
Upright	4	2318.0	1840.0
Upright	5	2277.0	1847.0
Inverted	1	2276.0	1877.0
Inverted	2	2365.0	2571.0
Inverted	3	2313.0	1781.0
Inverted	4	2333.0	2002.0
Inverted	5	2344.0	2572.0

B. Single Actuation Reproducibility after 6 Hour Delay

Ten canisters from each lot were tested for single actuation reproducibility following a 6 hour rest period after priming the canisters. Five canisters from each lot were stored upright and five canisters were stored inverted. The results for each lot are shown in Tables 2, 3, 4, 5, 6, and 7. The albuterol sulfate data from these tables was also compiled and is presented graphically in Figure 2.

For lots testing was discontinued after the first week. These lots exhibited the albuterol sulfate trend of being low for the first actuation 1 and high for the second actuation with a 6 hour rest after priming. The remaining lots do not exhibit this behavior and were tested through the life of the canister following the patient in use actuation protocol.

Table 2. Single Actuation Reproducibility for Lot Upright and Inverted Samples, Inherent Water

Albuterol Sulfate						
Lot /Orientation/Can	Week 1		Week 2		Week 3	
	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)
-Up-1	49.87	126.95	N/A	N/A	N/A	N/A
-Up-2	53.22	127.20	N/A	N/A	N/A	N/A
-Up-3	56.08	124.65	N/A	N/A	N/A	N/A
-Up-4	51.62	127.27	N/A	N/A	N/A	N/A
-Up-5	50.58	127.07	N/A	N/A	N/A	N/A
-Inv-1	78.10	151.04	N/A	N/A	N/A	N/A
-Inv-2	113.18	154.54	N/A	N/A	N/A	N/A
-Inv-3	88.07	174.11	N/A	N/A	N/A	N/A
-Inv-4	93.35	169.84	N/A	N/A	N/A	N/A
-Inv-5	70.53	161.62	N/A	N/A	N/A	N/A

Ipratropium Bromide						
Lot /Orientation/Can	Week 1		Week 2		Week 3	
	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)
-Up-1	95.24	98.92	N/A	N/A	N/A	N/A
-Up-2	93.13	104.19	N/A	N/A	N/A	N/A
-Up-3	99.05	102.11	N/A	N/A	N/A	N/A
-Up-4	96.32	101.88	N/A	N/A	N/A	N/A
-Up-5	98.14	96.52	N/A	N/A	N/A	N/A
-Inv-1	92.54	95.59	N/A	N/A	N/A	N/A
-Inv-2	94.69	91.53	N/A	N/A	N/A	N/A
-Inv-3	89.15	100.92	N/A	N/A	N/A	N/A
-Inv-4	93.30	93.63	N/A	N/A	N/A	N/A
-Inv-5	96.02	101.16	N/A	N/A	N/A	N/A

Table 3. Single Actuation Reproducibility for Lot 1
Upright and Inverted Samples, 800 ppm Water

Albuterol Sulfate						
Lot /Orientation/Can	Week 1		Week 2		Week 3	
	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)
-Up-1	48.60	137.69	N/A	N/A	N/A	N/A
-Up-2	49.35	123.03	N/A	N/A	N/A	N/A
-Up-3	59.65	123.56	N/A	N/A	N/A	N/A
-Up-4	49.85	128.45	N/A	N/A	N/A	N/A
-Up-5	45.63	128.28	N/A	N/A	N/A	N/A
-Inv-1	89.50	137.83	N/A	N/A	N/A	N/A
-Inv-2	63.97	145.05	N/A	N/A	N/A	N/A
-Inv-3	71.63	122.67	N/A	N/A	N/A	N/A
-Inv-4	75.94	126.01	N/A	N/A	N/A	N/A
-Inv-5	65.85	137.82	N/A	N/A	N/A	N/A

Ipratropium Bromide						
Lot /Orientation/Can	Week 1		Week 2		Week 3	
	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)
-Up-1	98.15	99.55	N/A	N/A	N/A	N/A
-Up-2	97.86	96.72	N/A	N/A	N/A	N/A
-Up-3	95.91	103.24	N/A	N/A	N/A	N/A
-Up-4	98.77	97.53	N/A	N/A	N/A	N/A
-Up-5	96.66	101.29	N/A	N/A	N/A	N/A
-Inv-1	95.75	98.33	N/A	N/A	N/A	N/A
-Inv-2	93.67	99.81	N/A	N/A	N/A	N/A
-Inv-3	97.13	97.87	N/A	N/A	N/A	N/A
-Inv-4	95.95	97.28	N/A	N/A	N/A	N/A
-Inv-5	95.27	102.27	N/A	N/A	N/A	N/A

Table 4. Single Actuation Reproducibility for Lot 5
Upright and Inverted Samples, 1000 ppm Water

Albuterol Sulfate						
Lot /Orientation/Can	Week 1		Week 2		Week 3	
	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)
-Up-1	71.63	110.75	N/A	N/A	N/A	N/A
-Up-2	56.02	130.26	N/A	N/A	N/A	N/A
-Up-3	51.97	126.82	N/A	N/A	N/A	N/A
-Up-4	52.41	124.41	N/A	N/A	N/A	N/A
-Up-5	80.63	104.43	N/A	N/A	N/A	N/A
-Inv-1	63.38	128.71	N/A	N/A	N/A	N/A
-Inv-2	65.70	128.20	N/A	N/A	N/A	N/A
-Inv-3	73.37	118.64	N/A	N/A	N/A	N/A
-Inv-4	77.65	121.92	N/A	N/A	N/A	N/A
-Inv-5	66.54	126.07	N/A	N/A	N/A	N/A

Ipratropium Bromide						
Lot /Orientation/Can	Week 1		Week 2		Week 3	
	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)
-Up-1	95.35	96.41	N/A	N/A	N/A	N/A
-Up-2	96.43	99.95	N/A	N/A	N/A	N/A
-Up-3	97.69	97.97	N/A	N/A	N/A	N/A
-Up-4	93.75	99.16	N/A	N/A	N/A	N/A
-Up-5	95.13	96.11	N/A	N/A	N/A	N/A
-Inv-1	95.56	100.24	N/A	N/A	N/A	N/A
-Inv-2	96.95	100.28	N/A	N/A	N/A	N/A
-Inv-3	97.81	97.64	N/A	N/A	N/A	N/A
-Inv-4	97.71	98.70	N/A	N/A	N/A	N/A
-Inv-5	96.17	100.76	N/A	N/A	N/A	N/A

Table 5. Single Actuation Reproducibility for Lot Upright and Inverted Samples, 1200 ppm Water

Albuterol Sulfate						
Lot /Orientation/Can	Week 1		Week 2		Week 3	
	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)
-Up-1	86.90	101.85	73.64	121.92	77.48	117.68
-Up-2	83.30	109.16	102.60	112.36	74.93	129.79
-Up-3	81.19	103.54	85.34	109.31	42.86	138.37
-Up-4	82.84	105.98	84.58	113.64	52.09	136.79
-Up-5	56.30	122.20	59.94	137.12	54.41	135.15
-Inv-1	88.93	99.61	78.58	123.30	72.41	128.21
-Inv-2	72.10	119.88	82.73	120.10	80.84	117.92
-Inv-3	84.10	113.51	77.30	129.43	65.37	127.29
-Inv-4	84.54	106.97	90.35	113.30	69.43	120.71
-Inv-5	76.56	119.07	80.61	119.43	71.24	124.34

Ipratropium Bromide						
Lot /Orientation/Can	Week 1		Week 2		Week 3	
	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)
-Up-1	96.35	99.24	99.01	97.95	100.61	100.79
-Up-2	94.35	103.75	94.91	104.14	106.38	102.25
-Up-3	95.98	98.17	96.63	97.03	96.92	102.54
-Up-4	94.38	102.45	95.96	97.79	98.10	105.19
-Up-5	101.78	97.93	101.37	102.52	102.73	107.02
-Inv-1	96.39	90.19	98.51	100.59	101.58	108.76
-Inv-2	100.10	100.60	99.82	102.67	103.73	107.96
-Inv-3	97.16	100.60	97.18	104.34	100.07	108.32
-Inv-4	95.58	97.43	98.27	102.32	105.41	108.44
-Inv-5	99.50	100.52	101.33	101.25	103.10	106.07

Table 6. Single Actuation Reproducibility for Lot 1
Upright and Inverted Samples, 1500 ppm Water

Albuterol Sulfate						
Lot./Orientation/Can	Week 1		Week 2		Week 3	
	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)
-Up-1	94.62	99.02	102.73	110.10	101.00	108.91
-Up-2	92.30	101.31	100.62	105.94	91.17	112.39
-Up-3	94.41	101.03	99.17	116.08	101.08	107.24
-Up-4	95.39	99.19	95.33	105.99	92.86	109.29
-Up-5	98.04	100.37	95.85	110.52	89.44	110.49
-Inv-1	96.36	99.38	92.49	109.67	83.09	107.79
-Inv-2	94.78	105.63	93.82	116.65	85.19	117.40
-Inv-3	98.08	101.14	101.80	107.13	94.68	110.60
-Inv-4	94.92	101.36	94.04	108.36	88.57	108.73
-Inv-5	93.20	99.04	99.38	110.70	94.67	102.19

Ipratropium Bromide						
Lot./Orientation/Can	Week 1		Week 2		Week 3	
	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)
-Up-1	97.57	97.84	95.93	100.56	104.01	105.51
-Up-2	96.13	99.37	99.04	97.10	102.07	107.00
-Up-3	101.21	98.24	99.87	102.88	107.59	107.83
-Up-4	98.40	98.62	98.13	97.41	101.62	104.50
-Up-5	100.59	98.85	97.67	101.23	101.67	106.88
-Inv-1	97.29	98.37	94.27	102.27	91.78	105.21
-Inv-2	97.21	102.94	98.97	105.40	103.99	108.79
-Inv-3	100.14	100.35	97.97	101.26	102.20	107.54
-Inv-4	97.44	101.24	98.73	100.17	103.00	107.15
-Inv-5	95.39	97.97	95.20	101.44	99.90	106.96

Table 7. Single Actuation Reproducibility for Lot Upright and Inverted Samples, 2500 ppm Water

Albuterol Sulfate						
Lot /Orientation/Can	Week 1		Week 2		Week 3	
	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)
-Up-1	95.51	96.18	93.06	106.82	89.02	98.71
-Up-2	91.40	98.26	97.25	100.72	91.40	96.23
-Up-3	97.37	98.65	99.53	96.12	90.59	103.09
-Up-4	95.08	95.98	91.04	103.12	79.05	103.87
-Up-5	95.89	100.90	104.42	95.22	92.35	100.06
-Inv-1	99.18	97.61	98.05	100.63	89.50	104.01
-Inv-2	98.00	99.87	103.83	105.87	87.10	97.13
-Inv-3	95.97	98.53	99.28	103.49	87.53	96.46
-Inv-4	97.42	97.94	95.65	102.85	88.18	97.42
-Inv-5	100.73	103.16	103.08	105.17	91.20	100.93

Ipratropium Bromide						
Lot /Orientation/Can	Week 1		Week 2		Week 3	
	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)
-Up-1	98.49	98.44	99.09	101.27	103.15	103.73
-Up-2	92.51	100.17	99.39	95.11	103.77	101.20
-Up-3	99.17	98.09	99.57	95.75	100.00	105.30
-Up-4	97.77	96.62	95.22	97.40	91.87	109.92
-Up-5	95.55	98.96	99.36	95.79	102.33	100.74
-Inv-1	98.09	99.33	97.88	100.19	102.34	110.94
-Inv-2	98.69	99.38	103.30	106.59	102.82	109.17
-Inv-3	94.24	101.02	96.22	103.06	100.14	108.23
-Inv-4	97.41	96.45	96.90	100.47	102.63	107.16
-Inv-5	96.72	102.32	102.22	105.63	104.23	110.85

C. Dose Uniformity after 6 Hour Delay

Ten canisters from each lot were tested for uniformity of dose (2 actuations) following a 6 hour rest period after priming the canisters. Five canisters from each lot were stored upright and five canisters were stored inverted. The results for each lot are shown in Tables 8, 9, 10, 11, 12, and 13. The albuterol sulfate data from these tables was also compiled and is presented graphically in Figures 3.

For lots testing was discontinued after the first week. These lots had exhibited poor single actuation reproducibility during the first week of testing. The remaining lots were tested through the life of the canister following the patient in use actuation protocol.

Table 8. Uniformity of Dose for Lot (Inherent Water), Upright and Inverted Samples

Lot/Orientation/Can	Week 1			Week 2			Week 3		
	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	Albuterol Sulfate (% of Theory)
Up/1	93.58	99.67	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Up/2	91.59	100.38	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Up/3	90.11	98.39	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Up/4	87.17	95.25	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Up/5	95.20	99.56	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Inv/1	148.63	97.29	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Inv/2	153.88	97.25	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Inv/3	168.93	102.22	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Inv/4	125.87	96.76	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Inv/5	118.27	99.42	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table 10. Uniformity of Dose for Lot (1000 ppm Water), Upright and Inverted Samples

Lot/Orientation/Can	Week 1			Week 2			Week 3		
	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	Albuterol Sulfate (% of Theory)
Upr1	94.82	101.07	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Upr2	92.18	97.01	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Upr3	94.90	102.35	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Upr4	87.00	94.65	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Upr5	91.39	97.60	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Inv1	103.68	100.80	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Inv2	101.18	100.45	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Inv3	101.69	100.84	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Inv4	97.50	98.91	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Inv5	99.93	99.46	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table 11. Uniformity of Dose for Lot (1200 ppm Water), Upright and Inverted Samples

1. Lot/Orientation/Can	Week 1			Week 2			Week 3		
	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)		Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)		Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	
Up/1	98.05	96.57		94.30	98.98		101.45	101.40	
Up/2	100.06	98.15		100.77	99.43		103.26	99.80	
Up/3	94.51	97.32		83.48	99.77		103.59	101.52	
Up/4	97.56	97.49		96.82	99.70		100.46	100.63	
Up/5	89.82	99.02		95.53	104.60		108.98	106.29	
Inv/1	99.90	100.52		97.95	101.21		103.23	104.73	
Inv/2	103.60	102.42		102.00	104.31		100.12	101.44	
Inv/3	94.77	92.73		97.57	100.38		97.78	102.36	
Inv/4	99.66	98.75		96.92	102.10		99.31	103.07	
Inv/5	102.07	99.49		95.21	100.01		96.91	104.22	

Table 12. Uniformity of Dose for Lot (1500 ppm Water), Upright and Inverted Samples

Lot/Orientation/Can	Week 1			Week 2			Week 3		
	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	Albuterol Sulfate (% of Theory)
Upr1	101.37	100.07	101.25	100.79	103.62	102.01			
Upr2	99.40	97.58	102.79	100.28	99.08	101.35			
Upr3	102.85	100.26	103.15	101.15	99.52	101.78			
Upr4	102.06	99.23	102.39	101.28	98.10	97.21			
Upr5	102.73	100.78	102.55	100.73	104.53	102.70			
Invr1	99.48	99.40	98.77	100.67	100.56	101.62			
Invr2	101.03	101.57	100.07	102.87	98.95	103.23			
Invr3	103.35	101.23	100.68	101.15	102.45	101.75			
Invr4	100.28	101.19	101.73	102.49	99.89	103.29			
Invr5	99.35	99.52	100.22	101.33	99.13	102.28			

Table 13. Uniformity of Dose for Lot (2500 ppm Water), Upright and Inverted Samples

Lot/Orientation/Can	Week 1			Week 2			Week 3		
	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	
Up/1	96.86	97.73	97.96	100.81	94.23	97.83			
Up/2	102.17	98.49	95.56	98.81	91.56	91.38			
Up/3	100.03	98.82	97.63	97.85	107.24	104.78			
Up/4	100.72	102.19	97.81	100.22	89.04	92.07			
Up/5	100.05	98.69	100.00	99.72	97.59	93.49			
Inv/1	99.99	99.29	96.75	101.20	92.36	99.61			
Inv/2	100.29	99.93	95.69	101.00	91.93	101.48			
Inv/3	100.94	99.01	97.78	100.57	92.58	100.08			
Inv/4	100.45	98.31	97.59	100.65	94.01	101.29			
Inv/5	104.03	101.43	101.26	103.90	96.34	103.60			

V. Conclusions

Water contents for all samples were in the expected ranges, although the measured results tended to be 100 – 150 ppm below target.

Single actuation results for lots with approximately 300 to 1000 ppm exhibited poor reproducibility between actuations at the beginning of the study. Testing on these canisters was discontinued after the first week of the study. Samples with 1200 ppm of water had only one can at the beginning of the study with poor reproducibility. Additional canisters from this lot started to exhibit poor reproducibility during the third week of the study. Samples with 1500 ppm water and 2500 ppm water exhibited good reproducibility between actuations throughout the study.

Dose uniformity results for all samples were within the expected ranges, with the exception of the inherent water inverted samples. These samples had 4 canisters out of 5 in excess of 125% of theory for drug delivery through the valve after a 6 hour pause. This trend was also observed for these canisters during single actuation reproducibility testing as well.

Total can assay results for the lots tested were within the expected range, with the exception of one inherent water inverted sample, which sprayed during sample preparation, resulting in low results for both albuterol sulfate and ipratropium bromide. This testing was added after the protocol was executed to confirm the analyte concentrations of the bulk solution in the canisters and that there were no losses in the metering chamber during actuation. There is good agreement of these results with the measured dose delivered through the valve, confirming that there is no loss occurring in the metering chamber during actuation.

The valve delivery results for all canisters tested were within expected ranges, with one exception for a canister near the end of the study, which was high and could not be explained. Since the value was high, it could not have been the result of a sticking valve, which produces low valve deliveries.

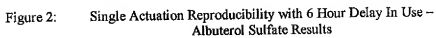


Figure 2: Single Actuation Reproducibility with 6 Hour Delay In Use – Albuterol Sulfate Results

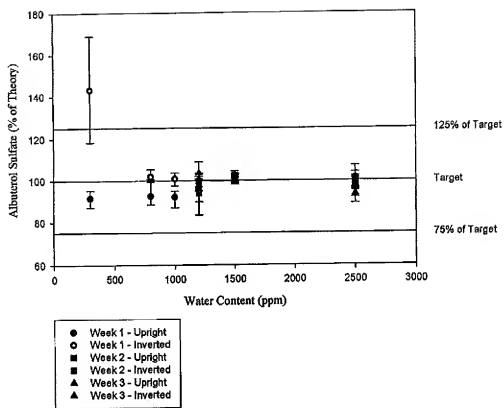


Figure 3: Uniformity of Dose with 6 Hour Delay In Use Study – Albuterol Sulfate Results

Attachment 1

Bespak 6 Hour Single Actuation and Dose through Life

Purpose:

The purpose of this protocol is to study the effect of water on single actuation reproducibility (SAR) and Dose through life (ca. 200 actuations). Samples were specially made to use the same concentrate, but have different water contents.

Samples:

AS Testing Number	Lot Number	Target ppm Water
AS 02-10-7515		Inherent
AS 02-10-7516		800
AS 02-10-7517		1000
AS 02-10-7518		1200
AS 02-10-7519		1500
AS 02-10-7520		2500

Five samples in each orientation (upright & Inverted) will be tested. This will result in a total of 60 canisters to be tested. Each canister will be tested according to the sampling protocol provided.

For all methods, calculate sample weights as follows: $W2 - W1 = \text{Sample Weight}$

W2 is the canister weight recorded immediately following each test point

W1 is the canister weight prior to testing (previous time point's W2.)

Wasting actuations will be performed using the alternate mouthpiece design. A delay of no less than 2 hours must occur between completion of previous wasting time point and

initiation of next wasting time point when multiple wasting sessions are required on the same day. Firing and shaking to be performed as outlined in the Uniformity of Dose procedure for wasting canisters. Do not clean the interior of the valve stem following wasting. Wasting will be performed per the provided sampling protocol.

Samples must equilibrate for 6 hours before any Uniformity of Dose sampling can be performed. The single actuation reproducibility protocol (SAR) requires that two single actuations be collected in separate containers where indicated. Do not shake canisters between the individual actuations for the SAR protocol. Uniformity of Dose samples will be collected per the provided sampling protocol.

If canisters containing lower levels of water (<1100 ppm) fail SAR during the first week of testing, then they will not be tested for the remainder of the study. Zero hour testing may be used to ensure that SAR failures are truly performance related.

Test Methods:

(Water) As per the sampling protocol below.

(Valve Delivery) With the exception that multiple actuations will be used for the determinations and multiple samples will be collected for each canister according to the sampling plan below. Weights will be recorded at the beginning of the study and after each actuation sequence

(Dose Uniformity) With the exception that samples will be collected after allowing the canisters to sit for 6 hours. Also samples will be collected using a single actuation reproducibility (SAR) protocol, which calls for allowing the sample to sit for 6 hours then collecting two single actuations in separate containers. Samples will be taken per the protocol below.

Start		
Day	Actuation Number	Action
Friday	1-5	Priming
	6-15	Clearing the Inlet tube
	16-20	Water Sample
Monday	21-24	Actuate to Waste Beg Day
	25&26	6 hr SAR *
	27-32	Actuate to Waste after SAR
Tuesday	33-36	Actuate to Waste Beg Day
	37-40	Actuate to Waste Mid Day
	41-44	Actuate to Waste End Day
Wednesday	45-48	Actuate to Waste Beg Day
	49&50	6 hr Dose *
	51-56	Actuate to Waste after Dose
Thursday	57-60	Actuate to Waste Beg Day
	61-64	Actuate to Waste Mid Day
	65-68	Actuate to Waste End Day
Friday	69-72	Actuate to Waste Beg Day
	73-76	Actuate to Waste Mid Day
	77-80	Actuate to Waste End Day

* 6 hrs after actuating to waste

Middle		
Day	Actuation Number	Action
Monday	81-84	Actuate to Waste Beg Day
	85-88	Actuate to Waste Mid Day
	89-92	Actuate to Waste End Day
Tuesday	93-96	Actuate to Waste Beg Day
	97&98	6 hr SAR *
	99-104	Actuate to Waste after SAR
Wednesday	105-108	Actuate to Waste Beg Day
	109&112	Actuate to Waste Mid Day
	113-116	Actuate to Waste End Day
Thursday	117-120	Actuate to Waste Beg Day
	121&122	6 hr Dose *
	123-128	Actuate to Waste after Dose
Friday	129-132	Actuate to Waste Beg Day
	133-136	Actuate to Waste Mid Day
	137-140	Actuate to Waste after SAR

* 6 hrs after actuating to waste

End		
Day	Actuation Number	Action
Monday	141-144	Actuate to Waste Beg Day
	145-148	Actuate to Waste Mid Day
	149-152	Actuate to Waste End Day
Tuesday	153-156	Actuate to Waste Beg Day
	157-160	Actuate to Waste Mid Day
	161-164	Actuate to Waste End Day
Wednesday	165-168	Actuate to Waste Beg Day
	169&170	6 hr Dose *
	171-174	Actuate to Waste after Dose
Thursday	175-178	Actuate to Waste Beg Day
	179-182	Actuate to Waste Mid Day
	183-186	Actuate to Waste End Day
Friday	187-190	Actuate to Waste Beg Day
	191&192	6 hr SAR *
Monday	193-202	Clear sample inlet tube
	203-207	Water – TP-00479

* 6 hrs after actuating to waste

Data Reporting:

Report the data using the Access Database provided.